REMARKS

Claims 1, 7, 13, 14, and 79 have been amended. Claim 12 has been cancelled without prejudice to its subsequent reintroduction into this application or its introduction into a related application. New claims 80-85 have been added. Upon entry of this paper, claims 1-11, 13, 14 and 79-85 will be pending and under consideration.

Support for the amendments to the claims can be found throughout the application as filed. For example, support for the amendment to claim 1 appears, for example, on page 23, lines 17-24 of the application as filed. Claim 7 has been amended to incorporate certain limitations of now cancelled claim 12. Claims 13 and 14 have been amended to modify antecedent basis in view of the cancellation of claim 12. Support for the amendments to claim 79 can be found, for example, on page 25, line 25, the paragraph bridging pages 14 and 15, and Figure 2 of the application as originally filed. New claims 80-85 correspond to claims 15-20, which were cancelled previously, but which the Examiner agreed to rejoin with the pending cartridge claims once those claims are in condition for allowance (see below). Applicants believe that the aforementioned amendments introduce no new matter.

The undersigned wishes to thank Examiners Bowers and Corcoran for their courtesy and for their insightful comments during an in-person interview with the undersigned and Dr. Norman Wainwright, an inventor of the claimed subject matter, which took place at the Office on June 27, 2007. During the interview, Dr. Wainwright provided the Office with an exemplary cartridge that embodies the invention. Dr. Wainwright described the components of the cartridge and its use. In addition, the pending independent claims together with certain proposed claim amendments and the prior art applied in the outstanding Office action were discussed during the interview. The undersigned understands that the proposed claim amendments will be attached to the interview summary that will be made of record in the application. The claim amendments and remarks concerning the claim amendments and applied art are discussed in more detail below. In addition, the undersigned asked that originally filed method claims 15-20 (now claims 80-85), which depend from certain of the cartridge claims currently under examination, be rejoined with the cartridge claims currently under examination. The Examiners indicated that the subject matter of method claims 15-20 (i.e., new claims 80-85) will be rejoined with the pending cartridge claims once the cartridge claims are in condition for allowance.

The outstanding rejections are addressed in the order in which they appear in the Office action.

Rejection of Claim 79 Under 35 U.S.C. § 102(b)

According to page 2 of the Office action, claim 79 presently stands rejected under 35 U.S.C. § 102(b) as being anticipated by International Patent Application Publication Number WO 99/53322 by Mahiout ("Mahiout"). Applicants respectfully traverse this rejection to the extent that is maintained over claim 79, as now amended, in view of the following remarks.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently, in a single prior art reference. (See, MPEP § 2131.) Applicants submit that Mahiout fails to meet this test.

As discussed in the previous Amendment and Response, Applicants submit that the Mahiout device is fundamentally different from the claimed invention. First, Mahiout describes the use of a device containing a test strip, where, in one embodiment (see, Figure 1 and Example 1), the device employs a "test strip" created within a capillary tube, and in a second embodiment (see, Figure 2 and Example 2), the device is based on a paper test strip. The Office has previously indicated that, for examination of the pending claims, Mahiout's capillary tube embodiment is more relevant than his paper test strip embodiment.

In Example 1 of Mahiout, the capillary tube is filled with beads referred to as "dried hydrophillic porous spherical material (200-500 μm)" (see, page 8 – Example 1). It appears that hemocyte (amebocyte) lysate is applied and dried on the polymeric powder (beads) (see, "Portion 1" on page 8). Afterwards, the beads with the lysate are placed within the capillary tube. Then, beads containing chromogenic substrate are introduced into a another region of the capillary tube next to portion 1 (see, "Portion 2" on page 8). The rest of the capillary tube is packed with beads containing other reagents to create the capillary tube shown in Figure 1.

Nowhere does Mahiout teach or suggest drying the lysate onto a fluid contacting surface of the capillary tube as is now required by amended claim 79. In Mahiout, the lysate is applied to beads, which are then packed in the capillary tube. This is clearly different from the claimed cartridge where the lysate is dried onto the fluid contacting surface of the capillary tube.

Applicants submit, therefore, that Mahiout fails to teach or suggest each and every element of independent claim 79, and the claims depending therefrom.

Applicants submit that the remarks provided below relating to the teachings of Mahiout, Tanaka, Numazawa, and Parce, as applied to independent claims 1 and/or 7, would also apply to amended claim 79. Nevertheless, in order to promote prosecution, claim 79 has been further amended to recite that the cartridge further comprises a pump port located downstream of the optical cell and a conduit connecting the optical cell and the pump port. Applicants submit that the skilled artisan aware of the art of record would not have been motivated to modify the teachings of the references applied in the Office action to produce a cartridge defined by amended claim 79.

Applicants believe that the cartridge of presently amended claim 79 is both novel and unobvious in view of the art of record. Accordingly, Applicants respectfully request that the rejection of claim 79 be reconsidered and withdrawn.

Rejection of Claims 1-6 Under 35 U.S.C. § 103

According to pages 3-5 of the outstanding Office action, claims 1-6 presently stand rejected under 35 U.S.C. § 103 as being obvious over Mahiout in view of U.S. Patent No. 5,550,030 to Tanaka *et al.* (Tanaka). Applicants respectfully traverse this rejection to the extent that it is maintained over claim 1, as amended, and the claims depending therefrom, in view of the following comments.

The standards for determining obviousness were included on pages 2 and 3 of the Office action. Applicants emphasize, however, that 35 U.S.C. §103 requires that the subject matter, taken as a whole, must be considered when evaluating the patentability of an invention.

The claimed invention is directed to a cartridge for determining the presence or amount of a microbial contaminant in a sample. The cartridge comprises: (i) a housing defining a fluid inlet port, an optical cell, and a conduit having a fluid contacting surface for providing fluid flow communication between the fluid inlet port and the optical cell; and (ii) a hemocyte lysate and an anti-flaking agent dried on a region of the fluid contacting surface of the conduit. When a sample is applied to the fluid inlet port, the sample traverses the region and solubilizes the

hemocyte lysate during transport to the optical cell. Applicants submit that cartridges embodied by the claimed invention permit one to quickly and efficiently run very sensitive assays for determining the presence or amount of a microbial contaminant, e.g., endotoxin, in a sample. For example, the claimed cartridges require that the user simply apply a sample of interest to the fluid inlet port before reading the result of the assay. In other words, no subsequent manipulation steps are necessary after the sample is applied to the cartridge in order to produce a result indicative of the presence and/or amount of a microbial contaminant in a sample.

Mahiout was discussed in the previous section and the comments (in particular the comments relating to the packed capillary tube embodiment) are reiterated here. The Office action acknowledges that in the Mahiout device, the "hemocyte lysate is not disposed directly on the fluid contacting surface of the conduit, but rather ... the lysate is disposed on a packing material within the conduit." Office action, page 4.

The Office, however, has relied upon the teachings of Tanaka to apparently make up for the deficiencies in Mahiout. For example, the Office alleges that Tanaka teaches that an endotoxin (Et)-sensitive factor (for example, a component of a hemocyte lysate) can be immobilized on an insoluble carrier to create a dry analytical instrument, and that it would have been beneficial to alter Mahout's apparatus in this way to alleviate any sample flow difficulties that result from the use of packing materials. Office action, page 4. Applicants respectfully disagree.

At the outset, Tanaka describes an Et-sensitive factor derived from a Limulus amebocyte immobilized on an insoluble carrier (see abstract). Tanaka, however, teaches that the Et-sensitive factor is permanently immobilized onto the solid carrier. For example, with regard to the term "immobilization" Tanaka states,

> [t]he terminology "immobilization" as used herein, taking an Et-sensitive factor for instance, means physical or chemical binding of an Et-sensitive factor to an insoluble carrier, which renders the Et-sensitive factor substantially insoluble in a reaction solution for Et assay while substantially maintaining its reactivity to Et. Col. 4, lines 16-21 (emphasis added).

In other words, the Et-specific factor does not become resolubilized (or released from the insoluble carrier) during the assay. This is made clear in Tanaka's examples. For example, Tanaka's Example 2 describes a cellulose ester membrane filter, which after being contacted with a mixture of lysate and dextran is then "thoroughly washed by passing 50 ml of a 0.02M tris-HCl buffer (pH 8.0) to obtain a cellulose ester filter having adsorbed thereon an Et-sensitive factor." (Col. 10, lines 24-27.) Furthermore, Examples 3, 5, 6, 7, 12, and 13 describe well-based assay formats, where the lysate is added to each well. In each example, either during the process of producing an insoluble carrier having an Et-sensitive factor disposed thereon or during the subsequent assay, the wells are washed, for example, with distilled water (DW). It appears that, even after washing, the Et-sensitive factor remains immobilized to the well. In addition, Example 4 describes the immobilization of an Et-sensitive factor onto vinyl polymer particles. Even after the particles were "thoroughly washed with a 0.1 M sodium phosphate buffer (pH 7.1)," the Et-sensitive factor remained coupled to the vinyl polymer particles.

Tanaka teaches immobilizing Et-sensitive factor to a solid support, but it appears, however, that the Et-sensitive factor is not intended to be released from the surface of the insoluble carrier support. This is fundamentally different from the claimed invention, which requires that when the sample of interest is applied to the claimed cartridge it traverses the region of the conduit having the hemocyte lysate dried thereon and solubilizes the hemocyte lysate during its transport to the optical cell. The hemocyte lysate of the claimed invention is not intended to remain bound to the surface of the conduit, rather, in order for the assay to work, the hemocyte lysate becomes solubilized by and mixed into the sample as it moves from the fluid inlet port to the optical cell. Applicants submit that if the Mahiout device was modified in accordance with the teachings of Tanaka it would render the Mahiout device (which requires the release of lysate from region 1 in Figure 1) inoperative. Accordingly, Applicants submit that the skilled artisan would not have been motivated to combine the teachings of Mahiout and Tanaka as suggested by the Office.

Nevertheless, in order to promote prosecution, Applicants have further amended claim 1 to specify that the hemocyte lysate is dried onto a region of the fluid contacting surface of the conduit with an anti-flaking agent. The advantages of drying the lysate with an anti-flaking

agent are described, for example, on page 23, lines 17-24 of the application as filed. Applicants believe that the concept of drying a hemocyte lysate on a fluid contacting surface of a conduit with an anti-flaking agent is neither taught nor suggested in the references being applied by the Office. Accordingly, Applicants submit that the applied references, among other things, fail to teach the subject matter of claim 1, taken as a whole. Furthermore, claims 2-6, which depend from and, therefore, incorporate the limitations of claim 1, are also novel and unobvious for the reasons discussed in connection with claim 1.

In its discussion of claims 4-6 on page 5 of the Office action, the Office suggests that Mahiout discloses that a preselected amount of an endotoxin is disposed in the first region of the fluid contacting surface of the conduit. Applicants disagree and submit that nowhere does Mahiout describe providing a conduit having a hemocyte lysate dried onto the conduit at the same time as an agent representative of a microbial contaminant (e.g., an endotoxin) is disposed on the fluid contacting surface of the conduit.

For the foregoing reasons, Applicants submit that the claimed cartridge, as defined by claims 1-6, as amended, would not have been obvious to the skilled artisan after reading the teachings of Mahiout and Tanaka. Accordingly, Applicants respectfully request that the rejection of claims 1-6 be reconsidered and withdrawn.

Rejection of Claims 7-14 Under 35 U.S.C. § 103

According to pages 5-7 of the outstanding Office action, claims 7-14 presently stand rejected under 35 U.S.C. § 103 as being obvious over Mahiout in view of Tanaka, and further in view of either EP 0 121 868 to Numazawa (Numazawa) or U.S. Patent No. 6,306,659 to Parce (Parce). Claim 12 has been cancelled without prejudice. Applicants respectfully traverse this rejection to the extent that it is maintained over claims 7-11, 13 and 14, as amended, in view of the following comments.

Independent claim 7, as amended, is directed to a cartridge for determining the presence or amount of a microbial contaminant in a sample. The cartridge comprises a housing defining (i) a first fluid inlet port, a first optical cell, and a first conduit having a fluid contacting surface for providing fluid flow communication between the first fluid inlet port and the first optical cell,

and (ii) a second fluid inlet port, a second optical cell, and a second conduit having a fluid contacting surface for providing fluid flow communication between the second fluid inlet port and the second optical cell. The cartridge further comprises hemocyte lysate dried on a first region of the fluid contacting surface of the first and second conduits, so that when a sample is applied to each inlet port, the sample traverses the regions containing the hemocyte lysate and solubilizes the hemocyte lysate during transport to the respective first and second optical cells. In addition, the cartridge further comprises an agent representative of a microbial contaminant (e.g., an endotoxin) dried on the fluid contacting surface of the first conduit.

Mahiout and Tanaka have been discussed previously together with the reasons Applicants believe that the skilled artisan would not have been motivated to combine their respective teachings. Specifically, Applicants believe that, for the reasons discussed above, if the Mahiout device was modified in accordance with the teachings of Tanaka it would render the Mahiout device inoperative.

The Office acknowledges that Mahiout only disclose the use of a single fluidic conduit comprising an inlet port, an optical cell and reagent. (Office action, page 5.) It appears that the Office is relying on the teachings of Numazawa or Parce to suggest that the skilled artisan would have been motivated to produce a cartridge containing a plurality of conduits where each conduit includes a fluid inlet port, an optical cell and a region defined by a hemocyte lysate. (Office action, page 6.) Applicants disagree.

As described in the previous Amendment and Response, Numazawa describes a transparent capillary tube for use in the detection of endotoxin. According to Numazawa, a transparent capillary tube format is advantageous because it obviates the need for transfer of a sample from a reaction vessel to a detection vessel (see, for example, the first full paragraph on page 2). Applicants submit, however, that Numazawa fails to teach or suggest a multi-conduit system.

For example, Applicants respectfully submit that Figures 5 and 7 and pages 9 and 10 in Numazawa describe a hermetically sealed membrane for packaging one or more capillary reaction tubes, particularly open-ended reaction tubes, and that Numazawa fails to teach or suggest a housing <u>defining</u> inlet ports, optical cells and conduits. For the sake of argument only,

even if one were to assume that Numazawa's membrane container is opened and that tests are performed using the multiple capillary reaction tubes while still disposed within the membrane container, the membrane container would not define fluid inlet ports, conduits, or optical cells, as is required by the housing of independent claim 7.

Although Parce describes various microfluidic devices and microfluidic methods, Parce fails to disclose incorporating a hemocyte lysate into its device. Rather, Parce is silent about the problems associated with developing a multi-conduit system containing a hemocyte lysate disposed in each conduit. Applicants submit that there is nothing in Parce that would motivate the skilled artisan to create a cartridge comprising a plurality of hemocyte lysate containing conduits.

Notwithstanding the foregoing, Applicants, in order to promote prosecution, have amended claim 7 to include the additional limitation that the cartridge further comprise an agent representative of a microbial contaminant (also referred to as a spike), for example, an endotoxin, dried on the fluid contacting surface of the first conduit. This concept appears, for example, on page 15, lines 20-23 of the application as filed. The advantages of including a spike for identifying the presence of hemocyte lysate enhancers or inhibitors in a test sample, are described in detail on page 22, line 8 – page 23, line 6 of the application as filed.

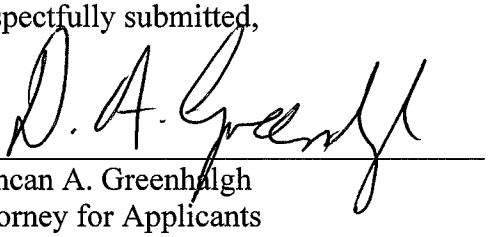
Applicants believe that the incorporation of a spike into a multi-conduit hemocyte lysate containing cartridge of the invention is neither taught nor suggested by any of the references made of record in the instant application. Furthermore, Applicants believe that the applied references, either alone or in combination, fail to teach of suggest the claimed subject matter, taken as a whole.

Claims 8-11, 13 and 14, depend from and therefore incorporate all the limitations of independent claim 7. Accordingly, Applicants believe that the subject matter of claims 8-11, 13 and 14 would have been unobvious to the skilled artisan for the same reasons as discussed for amended claim 7. In view of the foregoing, Applicants respectfully request that the rejection of claims 7-11, 13 and 14 be reconsidered and withdrawn.

CONCLUSION

Applicants believe that, in the view of the above amendments and comments, the pending claims are in condition for allowance. Early favorable action is respectfully solicited. The Office is invited to contact the undersigned with any questions about this submission.

Respectfully submitted,



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